Journal of Experimental and Clinical Medicine
https://dergipark.org.tr/omujecm

Research Article

J Exp Clin Med
2024; 41(1): 125-131
doi: 10.52142/omujecm.41.1.21

The effect of prognostic features of patients with chronic lymphocytic leukemia on overall survival and treatment-free survival: A single-center experience

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Received: 19.12.2023 • **Accepted/Published Online:** 14.03.2024 • **Final Version:** 29.03.2024

Abstract

Chronic lymphocytic leukemia (CLL) is a disease with a highly variable clinical spectrum and prognosis, and is more common in the elderly population. The identification of high-risk patients according to prognostic factors and the application of new treatment regimens have improved survival in CLL. The purpose of our study was to examine the effects of important prognostic factors on survival in patients with CLL in our patient population. Treatment-free survival (TFS) and overall survival (OS) analyses were performed in patients diagnosed with CLL between January 2000 and June 2013 according to clinical characteristics at the time of diagnosis, bone marrow infiltration pattern, lactate dehydrogenase (LDH) and beta 2-Microglobulin levels, CD38 expression and fluorescent insitu hybridization (FISH) findings. Two hundred and forty-five patients were evaluated. Presence of initial B symptom, Rai stage>I, Binet stage B and C, diffuse infiltration of bone marrow by lymphocytes, LDH, and beta 2-Microglobulin levels above upper limit of normal (ULN), and CD38 positivity shortened both TFS and OS ($p<0.05$). Also, age over 65 years, performance score of 2 and above, and del17p positivity shortened OS ($p<0.05$) but did not make a statistically significant difference in TFS. In multivariate analysis, it was determined that advanced age was an independent poor prognostic factor affecting OS, and Rai stage was an independent risk factor affecting TFS ($p<0.05$). When Rai stage was excluded, beta 2-Microglobulin and LDH were found to be negative prognostic risk factors affecting TFS independent of other factors. LDH level, which is not included in the international prognostic scoring system, was found to be a marker affecting TFS and OS in our study.

Keywords: chronic lymphocytic leukemia, prognosis, survival, lactate dehydrogenase, beta 2-microglobulin

1. Introduction

According to 2020 data, chronic lymphocytic leukemia (CLL) is the most common type of leukemia in western societies, with a median age at diagnosis of 70 years (1). CLL is characterized by clonal proliferation of mature CD5-positive B cells and symptoms develop when these mature lymphocytes accumulate in the blood, bone marrow, lymph nodes and spleen (2). Rai and Binet staging systems used in staging also have an important role in determining prognosis (3,4). Identification of prognostic risk factors is important for closer follow-up of high-risk patients. Currently, the CLL International Prognostic Index (CLL-IPI) is used to determine prognosis and includes age (65 years and younger vs >65 years), beta 2- Microglobulin level (≤3.5 mg/L vs >3.5 mg/L), TP53 status (no defect vs 17p deletion, TP53 mutation or both), immunoglobulin heavy chain (IGHV) mutation status (mutated vs unmutated) and clinical stage (RAI I-IV or Binet B-C) parameters are included in the scoring (5). According to CLL-IPI score, 5-year overall survival was 93.2% in low-risk patients, 79.3% in intermediate-risk patients, 63.3% in high-risk patients and 23.3% in very high-risk patients.

Different studies have shown that ZAP70 and CD38 expression (6) and biochemical markers such as serum lactate dehydrogenase level (7,8) have prognostic significance. There are studies showing that new mutations or deletions such as NOTCH1 and SF3B1 also affect prognosis with next generation sequencing (9,10).

In our study, we aimed to determine which parameters have prognostic significance in terms of treatment free survival (TFS) and overall survival (OS) in the 13-year follow-up of patients with CLL.

2. Materials and Methods

In the study, the files of 245 patients who were diagnosed with CLL/SLL or followed up in the Department of Internal Medicine, Division of Hematology, Hacettepe University between January 2000 and June 2013 and the information available in the patient record system were retrospectively

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analyzed. Informed consent was obtained from all patients or their first-degree relatives.

2.1. Clinical and Laboratory Data

In addition to the age and gender of the patients, LDH and beta 2-Microglobulin levels and absolute lymphocyte counts at the time of initial presentation were recorded. LDH level of >480 IU/L and beta 2-Microglobulin level of >2366 ng/ml were considered as high values. Besides, the results of bone marrow aspiration and biopsy performed for the diagnosis were also examined and recorded and the presence of nodular involvement or diffuse-diffuse involvement was examined because of its effect on prognosis. Immunophenotypic evaluation by flow cytometry, which was performed in most of the patients, and surface markers with prognostic significance were examined, and the results of cytogenetic examination and chromosome analysis obtained by Fluorescence in situ hybridization (FISH) method were also recorded in patients who could be evaluated. Physical examination and organomegaly and lymphadenopathies detected by imaging, if performed, the performance status of the patients according to Eastern Cooperative Oncology Group (ECOG) and whether they had B symptoms were evaluated.

2.2. Risk Stratification and Survival Endpoints

Staging of the patients was done according to Rai and Binet staging systems. Patients were divided into low, intermediate and high-risk groups according to modified Rai criteria.

Some concepts were defined as follows while performing survival analysis:

1. Overall Survival (OS): The period from the date of diagnosis to the date of last admission or death.

2. Treatment-Free Survival (TFS): The period from the date of diagnosis to the first line treatment (the period until the date of last follow-up or death for those who received no treatment)

The study was approved by the Hacettepe University Faculty of Medicine Non-Interventional Clinical Research Ethics Committee.

2.3. Statistical Analysis

Data analysis was done using the SPSS 18 (Statistical Package Social Science) statistical program. Categorical and continuous variables were compared using Chi-square and t-tests and ANOVA tests, respectively. Survival analyzes were performed using the Kaplan-Meier method. Comparison of survival rates was calculated with the Log-rank test. Multivariate analysis was performed with Cox-regression test. P<0.05 was considered statistically significant.

3. Results

Of the total 245 patients included in the study, 153 (62.4%) were male and 92 (37.6%) were female. The male/female ratio was calculated as 1.6/1. The median age of the patients, whose ages ranged from 30 to 88, was calculated as 62 years. 18% of the patients were in Rai stage 0, 50.3% in stage I-II and 22.7% in stage III-IV. FISH results were obtained in 55 patients (22.4%) and no chromosomal abnormality was detected in 31 (56%) of these patients. 17p deletion was found in 9 (16%) patients, one of whom also had trisomy 12 and one was t(14;18) positive, 13q14 (20%) deletion was found in 11 patients, t(11;14) in 1 patient, polysomy on chromosome 12 in 1 patient and 14q32 segregation in 1 patient. In 41 (16.7%) patients, chromosome analysis was obtained by cytogenetic examination, 22 (53%) had normal karyotype, 13 (32%) had no metaphase, 2 patients had clonality on chromosome 12, one patient had clonal loss on chromosome 13, one patient had derived 9, one patient had clonal loss on chromosome 11 and one patient had clonal loss on Y chromosome. CD38 was analyzed in 191 (77.9%) patients, 57 (30%) of whom were CD38 positive (CD38 of >20% was considered positive). It was observed that 80.7% of the CD38 positive patients were given treatment, while 19.3% were not given treatment. The median LDH level was 406 U/L±253 and the median beta 2-Microglobulin level was 2.817ng/ml±1.906. It was observed that 62.1% of the patients (152 patients) received at least one line of treatment during follow-up.

3.1. Prognostic Factors and Treatment-Free Survival

After a median follow-up of 52.4 months (±42.9), TFS was calculated as 9.5 months (±30.9 months). Univariate survival analysis of TFS with age, gender, bone marrow involvement, stage, CD38 positivity, LDH and beta 2-Microglobulin revealed that there was no significant correlation between age and gender and TFS, whereas TFS shortened with increasing Rai stage (p<0.05) (Table 1).

Bone marrow biopsy revealed that nodular infiltration of clonal B lymphocytes was associated with longer TFS compared to diffuse and mixed infiltration (Table 1). Patients with diffuse infiltration of the bone marrow had shorter treatment-free survival than those with nodular infiltration, even with Binet stages A and B (14.2 months [95% CI=2.1-26.2] vs 73.1 [95% CI=24.6-121], p<0.05).

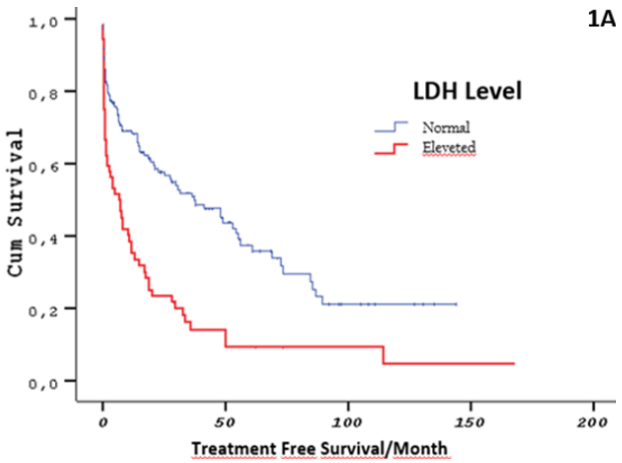

Fig. 1. LDH and Treatment-Free Survival

TFS was observed to be shorter in patients with LDH and beta 2-Microglobulin above reference values (p<0.001) (Table

1). While TFS=6.83 months (95%CI=2.2-11.4) in patients with high LDH; TFS was found to be 37.3 months (95% CI=21.4-53.3, p<0.001) in patients with normal LDH (Fig. 1). TFS=60.8 months (95% CI=44.3-77.3) in those with normal beta 2-Microglobulin, while TFS=11.4 months (95% CI=5.1-17.4; p<0.001) in those with high levels of beta 2-Microglobulin (Fig. 2).

According to flow cytometry results, TFS was shortened in patients with CD38 ≥20% and in patients with high ECOG performance score (Table 1).

Multivariate analysis to examine the effect of bone marrow infiltration pattern, ECOG status, CD38 positivity, Rai stage, beta 2-Microglobulin and LDH elevation on treatment-free survival revealed that Rai stage was an independent factor affecting treatment-free survival (p=0.003, Table 2, Model 1).

Table 1. Treatment-Free Survival and Overall Survival by Risk Factors

Parameter		Median TFS/month	*p value*	Median OS/month	*p value*
Gender	**Female** **Male**	16,6 19,8	*P=0,11*	119,4 100,7	*p=0,41*
Age	≤65 >65	18,5 17,4	*p=0,76*	136,9 87,1	*p<0.001*
B symptom	**Yes** **No**	2,8 35,8	*p<0.001*	77,1 119,4	*p=0.001*
RAI stage	0 I II III IV	NR 37,3 7,3 1,63 0,76	*p<0.001*	NR 110,9 107,3 70,2 61,3	*p<0.001*
Binet stage	**A** **B** **C**	50,1 7,3 1,1	*p<0.001*	136,9 107,3 63,7	*p<0.001*
ECOG	**0** **1** **≥2**	49,7 5,3 10,1	*p<0.001*	NR 108,7 61,3	*<0,001*
Pathology	Nodular Diffuse Mixed	73,1 5,7 19,2	*p<0.001*	NR 77,16 121	*p=0.004*
Hepatomegaly	**Yes** **No**	2,5 22,3	*p<0.001*	63,7 119,4	*p<0.001*
Splenomegaly	Yes No	2,5 37,3	*p<0.001*	67,6 136,9	*p<0.001*
LDH	**Normal** **Increased**	31,5 6,5	*p<0.001*	136,9 74,8	*P<0.001*
β2 microglobin	Normal Increased	60,8 10,1	*p<0.001*	NR 86,16	*P<0.001*
CD38	**Positive** **Negative**	6,5 29,6	*p<0.001*	72,2 136,9	*p=0.001*
17p del. **13q del.**				41,3 136,9	*p=0.036*

LDH: Lactate Dehydrogenase, ECOG: Eastern Cooperative Oncology Group, NR: Not Reached, TFS: Treatment free survival, OS: Overall survival.

Multivariate analysis with factors other than Rai stage (LDH and beta 2-Microglobulin levels, age group, bone marrow infiltration pattern, CD38 positivity) showed that elevated LDH (p=0.025) and beta 2-Microglobulin levels (p=0.043) were independent risk factors affecting treatment-free survival (Table 2, Model 2).

When the sites of extranodal involvement were analyzed, it was found that 27 patients (11%) had extranodal involvement, 3 patients had skin involvement, 4 patients had orbital involvement, 1 patient had testicular involvement, 4 patients had peritoneal involvement, 4 patients had pleural involvement, 3 patients had endobronchial involvement, 1

patient had lacrimal gland involvement, 2 patients had bone involvement and 2 patients had liver involvement. When the relationship between extranodal involvement and CD38 positivity, LDH elevation, beta 2-Microglobulin elevation and 17p deletion was analyzed, only a significant relationship was found between beta 2-Microglobulin above the reference value and extranodal involvement (p<0.038). Beta 2-Microglobulin levels were found to be elevated in 88.9% of patients with extranodal involvement, while this rate was 64.5% in patients without extranodal involvement.

Table 2. Multivariate Analysis of Prognostic Factors for Treatment Free Survival

Treatment Free Survival	*Independent Variables*	*Wald*	*p*	*H.R.*	*95,0% CI for H.R.*	
					Lower	**Upper**
Model 1	CD38 (Ref. negative)					
	CD38 positive	0.471	0.493	1.298	0.616	2.734
	beta 2-Microglobulin Level (Ref. Normal)					
	Elevated	2.848	0.091	0.425	0.157	1.148
	Bone marrow infiltration (Ref. Nodular)					
	Diffuse infiltration	0.250	0.617	0.743	0.232	2.380
	Diffuse and nodular infiltration	1.837	0.175	1.740	0.781	3.876
	ECOG performance status (Ref. 0)					
	ECOG 1	0.684	0.408	0.647	0.231	1.816
	ECOG ≥2	0.080	0.777	0.889	0.395	2.003
	RAI stage (ref. 0)					
	RAI 1	8.979	**0.003***	0.098	0.022	0.448
	RAI 2	0.910	0.340	0.548	0.159	1.885
	RAI 3	0.852	0.356	0.627	0.232	1.690
	RAI 4	0.801	0.371	1.607	0.569	4.538
	LDH Level (Ref. Normal)					
	Elevated	1.351	0.245	0.676	0.349	1.309
Model 2						
	beta 2-Microglobulin Level (Ref. Normal)					
	Elevated	4.100	**0.043***	0.477	0.233	0.977
	LDH Level (Ref. Normal)					
	Elevated	5.027	**0.025***	0.499	0.272	0.916
	CD38 (Ref. Negative)					
	Positive	0.324	0.569	0.839	0.459	1.534
	Bone Marrow Infiltration (Ref. Nodular)					
	Diffuse infiltration	0.469	0.494	0.690	0.238	1.998
	Diffuse and nodular infiltration	1.994	0.158	1.610	0.831	3.119
	Age (Ref. <65)					
	≥65	1.260	0.262	0.713	0.395	1.287

LDH: Lactate Dehydrogenase, ECOG: Eastern Cooperative Oncology Group, H.R: Hazard Ratio, CI: Confidence Interval

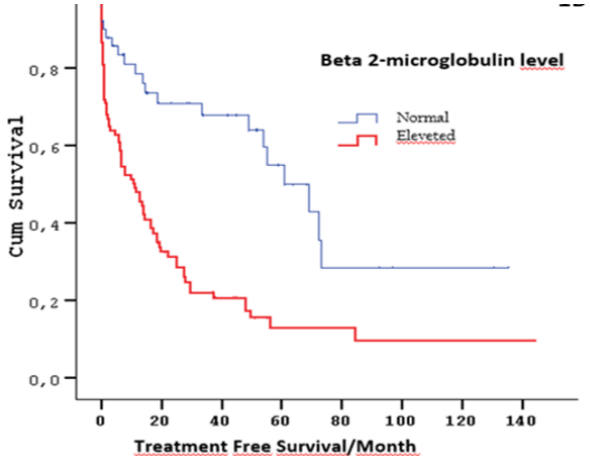

Fig. 2. Beta 2-Microglobulin and Treatment-Free Survival

3.2. Relationship between Prognostic Factors and Overall Survival

When the overall survival (OS) of the patients was analyzed, the median OS was 52.9 months, while patients diagnosed at a younger age (≤65 years) had a longer overall survival (136 months vs 87 months, 95% CI: 69-105 months, p<0.001).

OS shortened in Binet advanced stage patients, patients with high ECOG performance score, patients with CD38 positivity, patients with diffuse infiltration of bone marrow with lymphocytes, patients with 17p deletion, patients with elevated LDH and patients with elevated beta 2-Microglobulin (p<0.001) (Table 1). Mean OS was calculated as 74.8 months (95% CI: 56-92) in patients with high LDH levels and 136.9 months (95% CI: 94-179) in patients with normal LDH levels (p<0.01) (Fig. 3).

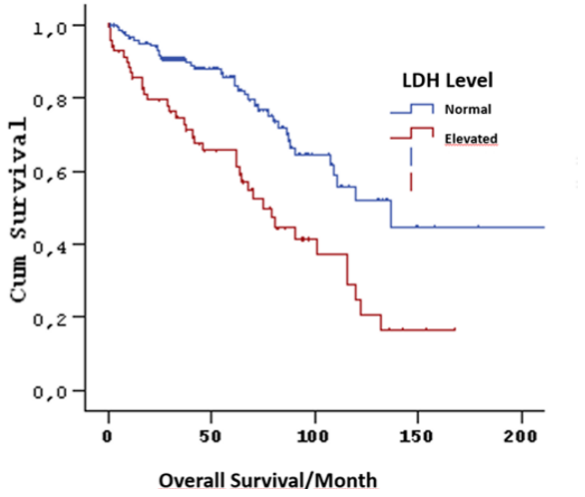

Fig. 3. Lactate Dehydrogenase and Overall Survival Time

It was also shown that elevated beta 2-Microglobulin levels were associated with short OS in patients with Binet stage A (Fig. 4). In patients with Binet stage A, patients with elevated beta 2-Microglobulin levels had shorter survival times than patients with normal beta 2-Microglobulin levels; median OS 110.9 months (95% CI=72.2-149.6 months) vs median OS > 200 months; p=0.012, respectively (Fig. 4).

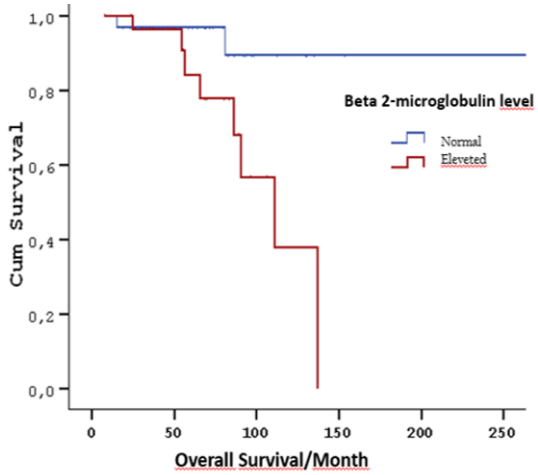

Fig. 4. Beta 2-Microglobulin Level and Survival in Patients with Binet Stage A

Multivariate analysis of the relationship between age at diagnosis (≤65, >65), LDH elevation at diagnosis, beta 2-Microglobulin elevation, bone marrow infiltration pattern, CD38 positivity and RAI stage and overall survival showed that only advanced age negatively affected overall survival independent of other parameters (p<0.05, Table 3, Model 1). Multivariate analysis of the relationship between beta 2-Microglobulin, Rai stage and bone marrow involvement pattern and survival showed that elevated beta 2-Microglobulin and advanced Rai stage (stage 3) negatively affected survival independent of bone marrow involvement pattern (p<0.05, Table 3, Model 2).

4. Discussion

Although chronic lymphocytic leukemia is a hematologic malignancy with an indolent course, improvement in survival can be achieved by closer follow-up of patients who will show an aggressive course with the identification of prognostic factors. The CLL-IPI scoring system was created in 2016 by combining the clinical findings of patients with biological and molecular parameters (5). It has a particularly significant role in identifying low-risk patients and managing high-risk patients (5). In our study, high beta 2-Microglobulin level, which is also included in the CLL-IPI scoring system, was shown to shorten treatment-free survival and overall survival independently of other parameters. Elevated beta 2-Microglobulin has been shown to be associated with poor prognosis even in patients with Binet stage A. Similar to the findings in our study, in the study conducted by Hallek et al., it was found that beta 2-Microglobulin had a predictive value independent of other factors in predicting progression-free survival, especially in early stage patients (11). Many previous studies have shown that elevated beta 2-Microglobulin is a negative prognostic risk factor for progression-free survival and overall survival in both previously untreated patients and relapsed patients (12–14). In a study investigating the effect of biomarkers on prognosis in 289 patients with CLL and, only beta 2-Microglobulin, one of the markers that can be measured in serum, was found to be an independent prognostic factor in

predicting overall survival (15).

Table 3. Multivariate Analysis of Prognostic Factors for Overall Survival

Overall Survival	*Independent Variables*	*Wald*	*p*	*H.R.*	*95,0% CI for H.R.*	
					Lower	**Upper**
Model 1	LDH level (Ref. Normal)					
	Elevated	1.368	0.242	0.590	0.244	1.429
	Beta 2-Microglobulin level (Ref. Normal)					
	Elevated	0.197	0.657	0.697	0.142	3.427
	CD38 (Ref. Negative)					
	Positive	0.126	0.722	1.172	0.488	2.818
	Bone Marrow Infiltration (Ref. Nodular)					
	Diffuse infiltration	0.003	0.954	0.000	0.000	0.000
	Diffuse and nodular infiltration	0.043	0.836	10.122	0.376	3.347
	Age (Ref. <65)					
	≥65	4.291	**0.038***	0.405	0.172	0.953
	RAI Stage					
	RAI 1	0.002	0.965	0.000	0.000	0.000
	RAI 2	1.633	0.201	0.376	0.084	1.685
	RAI 3	2.114	0.146	0.474	0.173	1.297
	RAI 4	2.336	0.126	0.369	0.103	1.325
Model 2						
	Beta 2-Microglobulin level (Ref. Normal)					
	Elevated	3.860	**0.049***	0.296	0.088	0.997
	Bone Marrow Infiltration (Ref. Nodular)					
	Diffuse infiltration	0.003	0.957	0.000	0.000	0.000
	Diffuse and nodular infiltration	0.064	0.801	1.110	0.493	2.501
	RAI Stage					
	RAI 1	0.002	0.961	0.000	0.000	0.000
	RAI 2	3.544	0.060	0.365	0.128	1.042
	RAI 3	4.760	**0.029**	0.379	0.159	0.906
	RAI 4	1.571	0.210	0.538	0.205	1.417

LDH: Lactate Dehydrogenase, H.R: Hazard Ratio, CI: Confidence Interval

In our study, increased LDH was also found to be a poor prognostic factor for treatment-free survival independent of other parameters. In a retrospective study conducted by Li et al., it was found that LDH elevation was an indicator of poor prognosis in terms of progression-free survival in CLL patients with 17p deletion (16). Another study showed that elevated LDH was associated with shorter progression-free survival, treatment-free survival and overall survival in previously untreated CLL patients with trisomy12 (8). In our study, the relationship between LDH elevation and survival in mutational subgroups could not be evaluated since few patients could be analyzed in terms of genetic mutations.

There are studies showing that the infiltration pattern of lymphocytes in the bone marrow is important for prognosis in CLL (17,18). However, nowadays, with the ability to detect chromosomal abnormalities and the widespread use of biomarkers, the pattern of bone marrow involvement has not been considered as an independent risk factor for prognosis. Although diffuse infiltration of bone marrow was found to negatively affect TFS and OS in our study, it was not found to be an independent risk factor in multivariate analysis including other prognostic markers.

Since targeted therapies were not yet in use as of the date of evaluation of patient data in our study, the findings cannot be generalized to patients receiving new treatment regimens. Although the number of patients was sufficient, the fact that immunoglobulin heavy chain mutation could not be analyzed and del17p or TP53 mutations were analyzed in a small number of patients are important limitations of our study.

When the results of our study were evaluated, it was observed that although LDH is not included in the CLL-IPI scoring system, it is a test that can be used to determine prognosis. Since LDH level is a practical test that can be

measured in almost every center, multicenter studies involving a larger number of patients, including the period when targeted therapies were used, should be conducted to evaluate its inclusion in prognostic scoring systems.

Conflict of Interest

All authors declare that they have no relevant financial or non-financial interests to disclose.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Acknowledgments

This article is based on the internal medicine specialty thesis of Nevin Alayvaz Aslan, supervised by Nilgün Sayınalp, and part of the article was presented as an oral presentation at the 7th "Karadeniz Hematoloji" Congress held on 2-3 July 2021.

Authors' contributions

Concept: N.A.A., Y.B., N.S., Design: N.A.A., Y.B., N.S., Data Collection or Processing: N.A.A., N.S., Analysis or Interpretation: N.A.A., Y.B. Literature Search: N.A.A., Y.B., N.S., Writing: N.A.A., Y.B., N.S.

Ethical Statement

The study was approved by the Hacettepe University Faculty of Medicine Non-Interventional Clinical Research Ethics Committee. (Ethics committee approval number GO 13/308-05, approval date 15/05/2013).

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